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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/600,060	07/10/2000	Neil Andrew Williams	CTH-03	6761

7590 07/29/2003

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EXAMINER
HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 07/29/2003

24

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/600,060	WILLIAMS ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49,53-56,59-64 and 66-82* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49, 53-56, 59-64 and 66-82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/13/03 has been entered.

2. Claims 49, 53-56, 59-64 and 66-82 are pending.

3. It is noted that claims 20-48, 50-52 and 57-58 are not withdrawn as stated in the amendment filed 6/13/03. However, claims 20-24, 26-30 and 40-48 have been canceled by amendment filed April 16, 2002. Claims 25 and 31-39 have been canceled by amendment filed 8/27/01. Claims 50-52, and 57-58 have been canceled by amendment filed 12/20/02. The difference between cancel claims and withdrawn claims is that claims that are withdrawn are still pending whereas canceled claims are no longer pending.

4. Newly submitted claims 49, 53-56, 59-64 and 66-82, drawn to a method for treating a subject for an allergic or hypersensitivity condition comprising administering to the subject an effective amount of an agent wherein the agent is *antibodies and derivatives of antibodies* that bind to GM1, are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claims 49, 53-56, 59-64 and 66-82 are drawn to a method of treating a subject for an allergic or hypersensitivity condition using antibodies and derivative of antibodies that bind to GM1, classified in Class 424, subclass 130.1. Claims 49, 53-56, 59-64 and 66-82 are drawn to a method of treating a subject for an allergic or hypersensitivity condition using agents such as Etx, Ctx, EtxB and CtxB that bind to GM1, classified in Class 424, subclass 184.1. The method of treating using distinct product such as antibodies versus agent such as polypeptide Etx, Ctx, EtxB and CtxB differ with respect to their structures, physiochemical properties and binding specificity. A search of one will not encompass the other. It is a burden to search more than one invention. Since applicant has received

an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 49, 53-56, 59-64 and 66-82 drawn to a method of treating a subject for an allergic or hypersensitivity condition using antibodies and derivative of antibodies that bind to GM1 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

5. Claims 49, 53-56, 59-64 and 66-82 drawn to a method of treating a subject for an allergic or hypersensitivity condition using an agent selected from the group consisting of Etx, Ctx, EtxB and CtxB that bind to GM1 are being acted upon in this Office Action.

6. Claims 49, 53-56, 59-64 and 66-82 are objected to because said claims are also drawn to a method of treating a subject for an allergic or hypersensitivity condition using antibodies and derivative of antibodies that bind to GM1, which are non-elected invention.

7. Claims 53-55, 59-60, 62-75 and 77-82 are objected to because "A" in said dependent claims should have been "The".

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 49, 53-56, 59-64 and 66-82 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for a method for treating a subject for asthma comprising administering to the subject an effective amount of an agent wherein the agent is EtxB that binds to GM1, **does not** reasonably provide enablement for (1) a method of treating a subject for *any* allergic or hypersensitivity condition such as atopic eczema, dermatitis, uticaria, hives, insect bite allergy, dietary allergy (peanut, fish, milk, wheat), drug allergies and contact hypersensitivity induced by insect, animal, plant or microbial allergens comprising administering the subject an effective amount of any agent such as Etx, Ctx, EtxB, CtxB, *any* antibodies and derivatives of *any* antibodies that bind to GM1, (2) the method of treating a subject for *any* "allergic or hypersensitivity

condition" such as atopic eczema, dermatitis, uticaria, hives, insect bit allergy, dietary allergy (peanut, fish, milk, wheat), drug allergies and contact hypersensitivity induced by insect, animal, plant or microbial allergens comprising administering the subject an effective amount of an agent wherein the agent is EtxB or CtxB, (3) a method of treating a subject for *any* allergic or hypersensitivity condition such as atopic eczema, dermatitis, uticaria, hives, insect bite allergy, dietary allergy (peanut, fish, milk, wheat), drug allergies and contact hypersensitivity induced by insect, animal, plant or microbial allergens comprising administering the subject an effective amount of *any* agent such as Etx, Ctx, EtxB, CtxB, *any* antibodies and derivatives of *any* antibodies that bind to GM1 and is not coupled to any antigen, (4) a method of treating a subject for *any* allergic or hypersensitivity condition such as atopic eczema, dermatitis, uticaria, hives, insect bite allergy, dietary allergy (peanut, fish, milk, wheat), drug allergies and contact hypersensitivity induced by insect, animal, plant (poison ivy) or microbial allergens comprising administering the subject an effective amount of any agent such as Etx, Ctx, *any* antibodies and derivatives of *any* antibodies that modify any GM1-associated activity and is not coupled to *any* "antigen", (5) the said method wherein the agent is CtxB, or EtxB, (6) the method of treating a subject for *any* allergic or hypersensitivity condition such as atopic eczema, dermatitis, uticaria, hives, insect bite allergy, dietary allergy (peanut, fish, milk, wheat), drug allergies and contact hypersensitivity induced by insect, animal, plant or microbial allergens comprising administering the subject an effective amount of any agent such as Etx, Ctx, *any* antibodies and derivatives of *any* antibodies that modify any GM1-associated activity and is not coupled to any antigen which is a treatment for asthma, and (7) a method for treating *any* allergic or hypersensitivity condition such as atopic eczema, dermatitis, uticaria, hives, insect bite allergy, dietary allergy (peanut, fish, milk, wheat), drug allergies and contact hypersensitivity induced by insect, animal, plant (poison ivy) or microbial allergens comprising administering the subject an effective amount of any agent such as Etx, Ctx, *any* antibodies and derivatives of *any* antibodies that modifies any GM1-associated activity wherein the agent is *any* antigen/allergen as set forth in claims 49, 53-56, 59-64 and 66-82. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only five agents such as Etx, Ctx, EtxB, CtxB, and EtxB (G33D) for screening for GM1 binding and GM1 associated activity in vitro. The specification discloses only one mutant which is EtxB (G33D) that is a derivative of EtxB, and a method of screening agent such as EtxB (G33D), EtxB that binds to GM1 wherein the EtxB (G33D) mutant is capable of modulating ganglioside associated activity by measuring the levels of cytokines such as IL-2, IL-4, IL-5, IL-10 and IFN-γ and antigen specific IgA *in vitro*. The specification defines the term "ganglioside associated activity" includes *any* one or more of modulating or immunomodulating a ganglioside receptor, modulating any signaling event prior to, during or subsequent to ganglioside receptor binding (page 15, lines 7-9). Further, the specification defines "agent capable of modulating a ganglioside associated activity" can be used to describe *any* agent, which acts as an immunomodulator or through interacting with a ganglioside (See page 17, lines 1-3). The specification defines the term "allergic condition" includes but not limited to asthma and the term "hypersensitivity condition" includes but is not limited to conditions such as contact hypersensitivity such as plant poison ivy (page 20). The specification defines the term "agent" can be one or more of an inorganic or organic chemical, as well as combination thereof, polypeptide, variant/homologue, derivative, fragment thereof so long as they retain the required immunomodulatory activity, it also includes mimics and equivalents and mutants thereof, other agents include antibodies to the target interaction components (page 21).

The specification does not teach how to make and use *any* "antibodies and derivatives of any antibodies that bind GM1, or *any* antibodies and derivatives of any antibodies that modify a*ny* GM1-associated activity because there is insufficient guidance as to chemical structure such as the amino acid sequence or epitope to which the antibodies bind, much less for treating any allergic or hypersensitivity condition using the

undisclosed antibody. Although the method of making antibody is known in the art, the specific epitope on GM1 to which the antibody bind that would modify any GM1 associated activity requires guidance, in turn would be useful for treating any allergic or hypersensitivity condition.

Kuby *et al* teach that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization with a peptide fragment derived from a full-length polypeptide may result in **antibody specificity** that differs from the antibody specificity directed against the native full-length polypeptide. Without the specific amino acid residues, it is unpredictable which undisclosed polypeptide would generate antibody that bind specifically to GM1 and modulates GM1 activity.

Abaza *et al* teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity of a protein with monoclonal antibody against the site (See abstract, in particular). Given the indefinite number of undisclosed antibodies, it is unpredictable which undisclosed antibodies, and derivatives thereof would bind specifically to GM1, modulates any GM1 activity and useful for treating any allergic or hypersensitivity condition.

Even if the agent is limited to Etx, Ctx, EtxB and CtxB, there is insufficient in vivo working example demonstrating that any Etx, Ctx, EtxB and CtxB mentioned above is effective for treating *any* allergic condition such as food allergy. The data provided in the declaration under 37 CFR 1.132 filed 6/13/03 by Neil Andrew Williams is limited to treating asthma using only EtxB and not just *any* allergic or hypersensitivity condition such as atopic eczema, dermatitis, uticaria, hives, insect bit allergy, dietary allergy (peanut, fish, milk, wheat), drug allergies and contact hypersensitivity induced by insect, animal, plant or microbial allergens. The Ovalbumin induced lung inflammation in murine is only a model for asthma (inhalation of allergen) and not for food allergy, drug allergy or even contact hypersensitivity. There is insufficient guidance as how effective the claimed method for treating any other allergy other than asthma since the route of allergen exposure is different than that of airway hyperreactivity to inhaled allergen in the asthma model. It has been well known to those skilled in the art at the time the invention was made that allergen specific antibody depends on the route of allergen exposure.

Further, Aman *et al*, of record, teach a mutant of cholera toxin B subunit (CtxB) such as CtxB (H57A) that has a single amino acid substitution from His to Ala lost its immunomodulatory activity although it still binds GM1 ganglioside (See entire document, abstract, in particular). It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions could result in substantially different pharmacological activities. Because of the lack of sufficient guidance and predictability in determining which epitope to which the antibody bind would lead to modifying which GM1-associated activity in vivo, it would require undue experimentation of even one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992). Given the indefinite number of undisclosed antibody and the lack of guidance as to which epitope of Ext, Ctx, CtxB and EtxB to which the antibody binds as well as the route of allergen exposure, it is unpredictable which undisclosed antibodies and derivative thereof would bind specifically to GM1, modulate any GM1 associated activity, in turn, would be useful for treating *any* allergic or hypersensitivity condition using the asthma model. Even if the antibody and derivative thereof bind to GM1, binding is not necessary equal to having a specific modifying activity, in turn, effective for treating any allergic conditions mentioned above. Further, there are no in vivo working example using *any* antibodies and derivatives thereof, Ctx, Etx, or CtxB for treating *any* allergic or hypersensitivity condition mentioned above. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Even if the agent is limited to Etx, there is no showing in the specification as filed that said agent could treat *any* allergic disorders such as food allergy, drug allergy, contact dermatitis using a model that is specific for asthma. "It is not sufficient to define the recombinant molecule by its principal biological activity, e.g. having protein A activity, because an alleged conception having no more specificity than that is simply a wish to know the identity of any material with that biological property." Colbert v. Lofdahl, 21 USPQ2d, 1068, 1071 (BPAI 1992).

For these reasons, it would require undue experimentation of even one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement

is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments in conjunction with the declaration under 37 C.F.R. 1.132 filed 6/13/03 by Neil Andrew Williams have been fully considered but are not found persuasive.

Applicants' position is that (1) "mutant or derivative thereof" has been removed from the claims. (2) The specification at page 20 has been amended to specify that "allergic conditions" or "hypersensitivity conditions" as the conditions listed in the Application at the time of filling. (3) Applicant has provided in vivo data as evidence of enablement for EtxB for treating asthma.

However, the amended claims still recite any allergic or any hypersensitivity condition. Further, the amended claims are drawn to a method of treating any allergic or hypersensitivity condition using any antibodies, and derivatives of any undisclosed antibodies for treating any allergic or hypersensitivity condition. The specification on page 20 defines the term "allergic condition" means asthma, allergic cough, allergic rhinitis, conjunctivitis, atopic eczema, dermatitis, uticaria, hives, insect bite allergy, dietary allergy (peanut, fish, milk, wheat, etc), and drug allergies. The term "hypersensitivity condition" means contact hypersensitivity induced by insect, animal, plant or microbial allergens. The specification does not teach how to make and use *any* "antibodies and derivatives of any antibodies that bind GM1, any antibodies that derivatives of any antibodies that modify any GM1-associated activity, much less for treating any allergic or hypersensitivity condition because there is insufficient guidance as to chemical structure such as the amino acid sequence or epitope to which any of the undisclosed antibodies bind. Although the method of making antibody is known in the art, the specific epitope on GM1 to which the antibody that would modify any GM1 associated activity requires guidance, in turn would be useful for treating any allergic or hypersensitivity condition.

Kuby *et al* teach that antibody epitopes (B cell epitopes) are not linear and are comprised of complex three-dimensional array of scattered residues which will fold into specific conformation that contribute to binding (See Kuby 1994, page 94, in particular). Immunization with a peptide fragment derived from a full-length polypeptide may result

in **antibody specificity** that differs from the antibody specificity directed against the native full-length polypeptide. Without the specific amino acid residues, it is unpredictable which undisclosed polypeptide would generate antibody that bind specifically to GM1 and modulates GM1 activity.

Abaza *et al* teach that even a single amino acid substitution outside the antigenic site can exert drastic effects on the reactivity of a protein with monoclonal antibody against the site (See abstract, in particular). Given the indefinite number of undisclosed antibodies, it is unpredictable which undisclosed antibodies, and derivatives thereof would bind specifically to GM1, modulates any GM1 activity and useful for treating any allergic or hypersensitivity condition.

Even if the agent is limited to EtxB, there is insufficient in vivo working example demonstrating that EtxB mentioned above is effective for treating any allergic condition such as food allergy. The data provided in the declaration under 37 CFR 1.132 is limited to treating asthma using only EtxB and not just *any* allergic or hypersensitivity condition such as atopic eczema, dermatitis, uticaria, hives, insect bit allergy, dietary allergy (peanut, fish, milk, wheat), drug allergies and contact hypersensitivity induced by insect, animal, plant or microbial allergens. The Ovalbumin induced lung inflammation in murine is only a model for asthma (inhalation of allergen) and not for food allergy, drug allergy or even contact hypersensitivity.

The data provided in the declaration under 37 CFR 1.132 filed 6/13/03 by Neil Andrew Williams is limited to treating asthma using only EtxB and not just *any* allergic or hypersensitivity condition such as atopic eczema, dermatitis, uticaria, hives, insect bit allergy, dietary allergy (peanut, fish, milk, wheat), drug allergies and contact hypersensitivity induced by insect, animal, plant or microbial allergens. The ovalbumin induced lung inflammation in murine is only a model for asthma (inhalation of allergen) and not for food allergy, drug allergy or even contact hypersensitivity. There is insufficient guidance as how effective the claimed method for treating any other allergy other than asthma since the route of allergen exposure is different than that of airway hyperreactivity to inhaled allergen in the asthma model. It has been well known to those skilled in the art at the time the invention was made that allergen specific antibody depends on the route of allergen exposure.

10. Claims 49, 53-56, 59-64 and 66-82 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) a method of treating a subject for *any* allergic or hypersensitivity condition such as atopic eczema, dermatitis, uticaria, hives, insect bite allergy, dietary allergy (peanut, fish, milk, wheat), drug allergies and contact hypersensitivity induced by insect, animal, plant or microbial allergens comprising administering the subject an effective amount of any agent such as Etx, Ctx, EtxB, CtxB, *any* antibodies and derivatives of *any* antibodies that bind to GM1, (2) the method of treating a subject for *any* "allergic or hypersensitivity condition" such as atopic eczema, dermatitis, uticaria, hives, insect bit allergy, dietary allergy (peanut, fish, milk, wheat), drug allergies and contact hypersensitivity induced by insect, animal, plant or microbial allergens comprising administering the subject an effective amount of an agent wherein the agent is EtxB or CtxB, (3) a method of treating a subject for *any* allergic or hypersensitivity condition such as atopic eczema, dermatitis, uticaria, hives, insect bite allergy, dietary allergy (peanut, fish, milk, wheat), drug allergies and contact hypersensitivity induced by insect, animal, plant or microbial allergens comprising administering the subject an effective amount of *any* agent such as Etx, Ctx, EtxB, CtxB, *any* antibodies and derivatives of *any* antibodies that bind to GM1 and is not coupled to any antigen, (4) a method of treating a subject for *any* allergic or hypersensitivity condition such as atopic eczema, dermatitis, uticaria, hives, insect bite allergy, dietary allergy (peanut, fish, milk, wheat), drug allergies and contact hypersensitivity induced by insect, animal, plant (poison ivy) or microbial allergens comprising administering the subject an effective amount of any agent such as Etx, Ctx, *any* antibodies and derivatives of *any* antibodies that modify any GM1-associated activity and is not coupled to *any* "antigen", (5) the said method wherein the agent is CtxB, or EtxB, (6) the method of treating a subject for *any* allergic or hypersensitivity condition such as atopic eczema, dermatitis, uticaria, hives, insect bite allergy, dietary allergy (peanut, fish, milk, wheat), drug allergies and contact hypersensitivity induced by insect, animal, plant or microbial allergens comprising administering the subject an effective amount of any agent such as Etx, Ctx, *any* antibodies and derivatives of *any* antibodies that modify any GM1-associated activity and is not coupled to any antigen which is a

treatment for asthma, and (7) a method for treating *any* allergic or hypersensitivity condition such as atopic eczema, dermatitis, uticaria, hives, insect bite allergy, dietary allergy (peanut, fish, milk, wheat), drug allergies and contact hypersensitivity induced by insect, animal, plant (poison ivy) or microbial allergens comprising administering the subject an effective amount of any agent such as Etx, Ctx, *any* antibodies and derivatives of *any* antibodies that modifies any GM1-associated activity wherein the agent is *any* antigen/allergen as set forth in claims 49, 53-56, 59-64 and 66-82.

The specification discloses only five agents such as Etx, Ctx, EtxB, CtxB, and EtxB (G33D) for screening for GM1 binding and GM1 associated activity in vitro. The specification discloses only one mutant which is EtxB (G33D) that is a derivative of EtxB, and a method of screening agent such as EtxB (G33D), EtxB that binds to GM1 wherein the EtxB (G33D) mutant is capable of modulating ganglioside associated activity by measuring the levels of cytokines such as IL-2, IL-4, IL-5, IL-10 and IFN-γ and antigen specific IgA *in vitro*. The specification defines the term "ganglioside associated activity" includes *any* one or more of modulating or immunomodulating a ganglioside receptor, modulating any signaling event prior to, during or subsequent to ganglioside receptor binding (page 15, lines 7-9). Further, the specification defines "agent capable of modulating a ganglioside associated activity" can be used to describe *any* agent, which acts as an immunomodulator through interacting with a ganglioside (See page 17, lines 1-3). The specification defines the term "allergic condition" includes but not limited to asthma and the term "hypersensitivity condition" includes but is not limited to conditions such as contact hypersensitivity such as plant poison ivy (page 20). The specification defines the term "agent" can be one or more of an inorganic or organic chemical, as well as combination thereof, polypeptide, variant/homologue, derivative, fragment thereof so long as they retain the required immunomodulatory activity, it also includes mimics and equivalents and mutants thereof, other agents include antibodies to the target interaction components (page 21).

With the exception of the specific Etx, Ctx, EtxB, CtxB, and EtxB (G33D) mentioned above for in vitro screening assays, and the specific EtxB for treating asthma provided in the declaration under 37 CFR 1.132 filed 6/13/03 by Neil Andrew Williams, there is insufficient written description about the structure associated with function of (1) *any* "antibodies" and "derivatives" of *any* antibodies because the binding specificity, the epitope to which the antibody binds, in turn, the antibodies and derivatives thereof that

modulates any GM1-associated activity for the method of treating *any* allergic condition are not adequately described. Further, there is insufficient written description about the structure associated with function of any "antigen" since not all antigen are allergen. Finally, even if the agent is limited to EtxB for the claimed method, the method of treating *any* allergic or hypersensitivity condition such as atopic eczema, dermatitis, uticaria, hives, insect bite allergy, dietary allergy (peanut, fish, milk, wheat), drug allergies and contact hypersensitivity induced by insect, animal, plant or microbial allergens using only the Ovalbumin induced airway hypersensitivity as a model for asthma is not adequately described.

Given the lack of a written description of *any* additional representative species of antibodies, derivatives of antibody for treating any allergic condition, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 6/13/03 have been fully considered but are not found persuasive.

Applicants' position is that the claims have been amended.

However, the amended claims still recite any allergic or any hypersensitivity condition. Further, the amended claims are drawn to a method of treating any allergic or hypersensitivity condition using any antibodies, and derivatives of any undisclosed antibodies for treating any allergic or hypersensitivity condition. The specification on page 20 defines the term "allergic condition" means asthma, allergic cough, allergic rhinitis, conjunctivitis, atopic eczema, dermatitis, uticaria, hives, insect bite allergy, dietary allergy (peanut, fish, milk, wheat, etc), and drug allergies. The term "hypersensitivity condition" means contact hypersensitivity induced by insect, animal, plant or microbial allergens. There is insufficient written description about the structure associated with function of (1) *any* "antibodies" and "derivatives" of *any* antibodies because the binding specificity, the epitope to which the antibody binds, in turn, the antibodies and derivatives thereof that modulates any GM1-associated activity for the method of treating *any* allergic condition are not adequately described. Further, there is

insufficient written description about the structure associated with function of any "antigen" since not all antigen are allergen. Finally, even if the agent is limited to EtxB for the claimed method, the method of treating *any* allergic or hypersensitivity condition such as atopic eczema, dermatitis, uticaria, hives, insect bite allergy, dietary allergy (peanut, fish, milk, wheat), drug allergies and contact hypersensitivity induced by insect, animal, plant or microbial allergens using only the Ovalbumin induced airway hypersensitivity as a model for asthma is not adequately described.

Given the lack of a written description of *any* additional representative species of antibodies, derivatives of antibody for treating any allergic condition, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.*

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 49, 53, 55, 56, 59, 61-63, 71, 76, 79 and 80 are rejected under 35 U.S.C. 103(a) as being unpatentable WO 95/10301 publication (of record, April 1995, PTO 1449) or Tumura *et al* (of record, Vaccine 15(2): 225-229, 1997) each in view of WO 97/02045 publication (of record, Jan 1997, PTO 1449) or Nashar *et al* (of record, Proc Natl Acad Sci 93: 226-30, Jan 1996; PTO 1449).

The WO 95/10301 publication teaches a method for treating a subject for hypersensitivity condition such as allergy or delayed-type-hypersensitivity (DTH) reactions to human gamma globulins comprising administering to the subject such as mice an effective amount of an agent such as B subunit of *E coli* heat-labile enterotoxin (LTB) or the B subunit of cholera toxin (CTB) conjugated to an antigen such as ragweed pollen (page 14, line 16), or human gamma globulins or Red blood cell (RBC) (See pages 23, 24, Example 1, pages 26 and 32, Tables 2-9, claims 16, 1-5, 8, 9, in particular). The reference LTB and CTB bind to GM1 (See page 17, lines 23-30, in particular) and have an effect on GM1 mediated intracellular signaling events such as prolonged graft survival, suppression of EAE (See pages 28-29, in particular). The reference LTB and CTB are the same as the claimed EtxB and CtxB, respectively. The WO 95/10301 publication teaches that mucosally induced systemic tolerance can be utilized to reduce or suppress immune responses not only against foreign antigen but also to autoantigen.

Tamura *et al* teach a method for treating a subject for hypersensitivity condition such as allergy or delayed-type-hypersensitivity (DTH) reactions comprising administering to the subject such as mice an effective amount of an agent such as B subunit of *E coli* heat-labile enterotoxin (LTB) or LT coupled or conjugated to an antigen such as ovalbumin (See abstract, page 227, column 1, in particular). The reference LTB and CTB bind to GM1 (See page 226, Preparation of LTB-LT conjugated antigen, in particular). The reference LT and LTB are the same as the claimed Etx and EtxB, respectively. The reference ovalbumin (OVA) coupled to LTB suppresses the induction of both DTH and IgE antibody responses (See page 225, column 2,Table 1, in particular). Tamura *et al* teach LTB-coupled OVA is useful for suppressing the induction of both DHT and IgE antibody responses and LTB as well as CTB can serve as a powerful carrier induction of immunological tolerance (See page 228, column 1, first full paragraph, in particular).

The claimed invention as recited in claim 56 differs from the teachings of references only that the agent modifies a GM1-assciated activity wherein the agent is not coupled to an antigen.

The claimed invention as recited in claim 61 differs from the teachings of references only that the agent is selected from the group consisting of CtxB, EtxB or a mutant or derivatives thereof that modifies a GM1-associated activity and is not coupled to an antigen.

The WO 97/02045 publication teaches a method for treating a subject comprising administering to the subject such as mice an effective amount of an agent such as B subunit of *E coli* heat-labile enterotoxin (EtxB) or a derivative of EtxB such as EtxB (G33D) which is also a mutant of EtxB having Gly-33 to Asp substitution, and an antigen such as OVA, which is also an allergen, in a mixture (not coupled) (See page 16, in particular). The reference method is useful for induction of tolerance to foreign antigenic determinant (See claim 16 of WO 97/02045, in particular).

Nashar *et al* teach agent such as E. Coli heat-labile enterotoxin (Etx) which is closely related homologue cholera toxin (Ctx) EtxB and mutant such as EtxB (G33D) and their respective B subunits are potent mucosal and systemic immunogens and potential carriers (See page 226, column 1, in particular). The reference B subunits Etx and Ctx bind to GM1 and modulate immune response such as serum antibody response (See page 228, Fig 2, in particular). Nashar *et al* further teach mutant or derivative of Etx such as EtxB (G33D), which is a mutant having a Gly to Asp substitution at residue 33; the reference EtxB (G33D) fails to bind to GM1 but has an effect on GM1 mediated intracellular signaling events such as lymphocyte proliferation (Table 1, in particular). Nashar *et al* teach the reference ExtB stimulates B and T cells activation (See Fig 4, in particular) while EtxB (G33D) mutant decreases B and T cell activation, but increases IFNγ production (See Table 2, in particular). Further, the reference teaches EtxB but not EtxB (G33D) causes complete depletion of CD8+ cells by apoptosis (See page 230, column 1, second full paragraph, in particular). Nashar *et al* teach that the potent immunogenicity of the reference agents is dependent not only on efficient receptor-mediated uptake but also on direct receptor-mediated immunomodulation of lymphocyte subsets (See Abstract, in particular).

Therefore, it would have been obvious to one ordinary skill in the art at the time the invention was made to treat allergic condition as taught by the WO 95/10301 publication or Tamura *et al* by administering an effective amount of an agent such as LTB (EtxB) or CTB (CtxB) as taught by the WO 95/10301 publication or the EtxB as taught by Tamura *et al* or the EtxB derivative or mutant such as EtxB (G33D) or agent such as EtxB as taught by the WO 97/02045 publication or the Ctx and EtxB (G33D) as taught by Nashar *et al* either conjugated or unconjugated to any allergen as taught by Tamura *et al* for a method for treating a subject for allergic or hypersensitivity condition.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the WO 97/02045 publication teaches the reference agent such as B subunit of *E coli* heat-labile enterotoxin (EtxB) or a derivative of EtxB such as EtxB (G33D) is useful for induction of tolerance to foreign antigenic determinant (See claim 16 of WO 97/02045, in particular). Tamura *et al* teach that administering Escherichia coli heat-labile B subunit (LTB), also known as EtxB conjugated to allergen is useful for induced tolerance by suppression of delayed-type hypersensitivity and IgE antibody response to allergen such as ovalbumin (See abstract, Figure 1, Table 1, Figure 2, page 225, second column, in particular). The recitation of "unconjugate antigen/allergen" is an obvious variation of the teachings of Tamura *et al* and WO 95/10301 publication because all conjugated allergens are derived from unconjugated allergen. Nashar *et al* teach that the reference agents' potent immunogenicity is dependent not only on efficient receptor-mediated uptake but also on direct receptor-mediated immunomodulation of lymphocyte subsets (See Abstract, in particular). The recitation of effective amount is within the purview of one ordinary skill in the allergy art at the time the invention was made to administer the appropriate dose to the subject.

Applicants' arguments filed 6/13/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) the claimed invention relates to agents that bind to GM1 or modify a GM1-associated activity which are employed to treat asthma, allergic cough, allergic rhinitis, and conjunctivitis, atopic eczema and dermatitis, uticaria, hives, insect bite allergy, dietary allergy, drug allergies, and contact sensitivity to plant allergens. (2) The references when combined fail to teach an effective amount of an agent that is selected from the group consisting of Etx, Ctx, EtxB, CtxB, antibodies and derivatives of antibodies that bind to GM1. (3) WO 95/10301 does not disclose administering an effective amount of agent to solve the problems of treating allergic or contact hypersensitivity conditions. (4) The WO97/02045 fails to teach the step of administering to the subject an effective amount of an agent that is selected fro the group consisting of Etx, Ctx, EtxB, CtxB, antibodies and derivatives of antibodies that that bind to GM1. The reference is particularly concerned with treating autoimmune disease. (5)

Nashir fails to teach or suggest an effective amount of an agent that is selected from the group consisting of Etx, Ctx, EtxB, CtxB, antibodies and derivatives of antibodies that bind to GM1. Nowhere does Nashir teach or suggest an effective amount of these specific agents to treat allergic or hypersensitivity conditions. (6) The experimental results previously provided by Applicants' research group in the WO97/02045 and Nashar and Tamura et al do not suggest Applicants' claimed invention. On the contrary, they point away from the invention by suggesting that GM1 binding agents would not find use in the treatment of allergic/hypersensitivity conditions.

In response to Applicants' argument that the references when combined fail to teach an effective amount of an agent that is selected from the group consisting of Etx, Ctx, EtxB, CtxB, antibodies and derivatives of antibodies that bind to GM1, the specific effective amount of any agent mentioned above is not recited in the claims. Further, it is within the purview of one ordinary skilled in the allergy art at the time the invention was made to administer an effective amount to a subject in need of such treatment. Tamura *et al* teach administering Escherichia coli heat-labile B subunit (LTB), also known as EtxB conjugated to allergen induced tolerance by suppression of delayed-type hypersensitivity and IgE antibody response to allergen such as ovalbumin (See abstract, Figure 1, Table 1, Figure 2, in particular). The reference method is useful for abrogating unwanted immune responses and induction of tolerance toward allergen (See page 225, second column, in particular). Tamura et al further teach that intranasal administering LTB-OVA together with free LT or LTB-OVA, or a mixture of OVA and LTB (unconjugated) three days before systemic immunization. The results shown in Fig 2 indicate that the mixture of OVA and LTB treated group still inhibit DTH while the free LT abrogated the suppression of both DTH and IgE responses.

In contrast to Applicants' assertion that there is no disclosure of suggestion in Tamura et al that EtxB can work in the absence of a conjugated antigen, Tamura et al that EtxB-OVA conjugates can prevent allergy (See Table 1, page 227, in particular). Tamura et al further teach that intranasal administering LTB-OVA together with free LT or LTB-OVA, or a mixture of **OVA and LTB (unconjugated)** three days before systemic immunization. The results shown in Fig 2 indicate that the mixture of OVA and LTB treated group still inhibit DTH while the free LT abrogated the suppression of both DTH and IgE responses.

In contrast to Applicants' assertion that the experimental result in WO97/02045 would suggest that GM1 binding agent such as EtxB would not find use in the treatment of allergic conditions, the WO 97/02045 publication teaches a method for treating a subject comprising administering to the subject such as mice an effective amount of an agent such as B subunit of *E coli* heat-labile enterotoxin (EtxB) or a derivative of EtxB such as EtxB (G33D) which is also a mutant of EtxB having Gly-33 to Asp substitution, and an antigen such as OVA, which is also an allergen, in a mixture (not coupled) (See page 16, in particular). The reference method is useful for induction of tolerance to foreign antigenic determinant because it induces apoptosis in CD8+ T cell population (See claim 16 of WO 97/02045, in particular) as well as increase IFNγ and IL-2 production which can be detected in the supernatants from EtxB or EtxB (G33D) cocultured with lymphocyte (See Table 2 on page 41, page 31, lines 12-13, in particular). Both IFNγ and IL-2 are classical Th1 cytokine that are known to cross-regulate Th2 immune response.

In contrast to Applicants' assertion that there was clear technical prejudice in the art before the priority date of the present invention against using an agent such as EtxB to prevent and/or treat an allergic and/or hypersensitivity condition, Tamura et al, of record, clearly teach that the key difference between LT (holotoxin) or LTB lies within the B subunit since free LT coadministering with LTB-OVA abrogated the suppression of both DTH and IgE responses (Fig 2, page 228, in particular). Tamura et al further teach that oral or nasal tolerance to some antigen is abrogated by the oral or nasal administration of antigen coupled to or together with cholera toxin/cholera toxin B subunit (CT/CTB) containing trace amount of CT (See page 225, column 1, in particular).

14. Claims 54, 60, 64, 66-70, 72-75, 77-78, 81 and 82 are rejected under 35 U.S.C. 103(a) as being unpatentable WO 95/10301 publication (of record, April 1995, PTO 1449) or Tumura *et al* (of record, Vaccine 15(2): 225-229, 1997) each in view of WO 97/02045 publication (of record, Jan 1997, PTO 1449) or Nashar *et al* (of record, Proc Natl Acad Sci 93: 226-30, Jan 1996; PTO 1449) as applied to claims 49, 53, 55, 56, 59, 61-63, 71, 76, 79 and 80 mentioned above and further in view of Roitt *et al* (of record, in Immunology, 2nd edition, pages 19.1-19.3, 1989, PTO 892) and Patterson *et al* (of record, J immunol 117(1): 97-101, July 1976, PTO 892).

The combined teachings of the WO 95/10301 publication, the WO 97/02045 publication, Nashar *et al* and Tumura *et al* have been discussed supra.

The claimed invention as recited in claims 54, 60, 64, 66 and 81 differs from the teachings of the references only by the recitation that the treatment is for asthma.

The claimed invention as recited in claims 67, 74 and 78 differs from the teachings of the references only by the recitation that the hypersensitivity condition is contact sensitivity.

The claimed invention as recited in claims 66, 69 73 and 77 differs from the teachings of the references only by the recitation that the allergic condition is asthma, allergic rhinitis, atopic eczema, uticaria, insect bite allergy.

The claimed invention as recited in claims 68, 72, 75 and 82 differs from the teachings of the references only by the recitation that the treatment is for allergic rhinitis.

The claimed invention as recited in claim 70 differs from the teachings of the references only by that the method wherein the hypersensitivity condition is contact sensitivity induced by plant poison ivy.

Roitt *et al* teach hypersensitivity (type I) such as asthma, eczema, hay fever, urticaria insect bite allergy such as bee venom is characterized by an allergic reaction immediately following contact (contact hypersensitivity) with an allergen (See page 19.2, in particular). Roitt *et al* teach IgE levels are often raised in allergic disease (See page 19.1, page 19.3, column 2, in particular) and the production of IgE is controlled by IL-4, which is a Th2 cytokine (See page 19.5, column 1, in particular). Roitt *et al* further teach the development of drugs, which inhibit the action of IL-4, may have important therapeutic potential for controlling IgE responses and allergy (See page 19.5, column 1, in particular).

Patterson *et al* teach cholera toxin (Ctx) inhibits IgE production (See abstract, in particular).

Therefore, it would have been obvious to one ordinary skill in the art at the time the invention was made to include asthma as one of the hypersensitivity condition as taught by Roitt *et al* using the agent such as LTB (EtxB) or CTB (CtxB) as taught by the WO 95/10301 publication or the agent such as EtxB (G33D) or EtxB as taught by the WO 97/02045 publication or the agent such as Ctx and EtxB (G33D) as taught by Nashar *et al* or the agent such as CtB or LtB either conjugated or unconjugated to any allergen as taught by Tamura et al for a method for treating a subject for allergic or hypersensitivity

condition as taught by the WO 95/10301 publication and Tamura et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Roitt *et al* teach the development of drugs which inhibit the action of IL-4 may have important therapeutic potential for controlling IgE responses and allergy (See page 19.5, column 1, in particular). Claim 70 is included in this rejection since it is within the purview of one skill in the art at the time the invention was made because Roitt *et al* teach hypersensitivity (type I) such as asthma, eczema, hay fever, urticaria insect bite allergy such as bee venom is characterized by an allergic reaction immediately following contact (contact hypersensitivity) with an allergen (See page 19.2, in particular) and the development of drugs which inhibit the action of IL-4 may have important therapeutic potential for controlling IgE responses and allergy (See page 19.5, column 1, in particular).

Applicants' arguments filed 6/13/03 have been fully considered but are not found persuasive.

Applicants' position is that (1) Roitte et al teach hypersensitivity in general terms. Patterson et al attempted to determine if human peripheral blood lymphocytes cultured in vitro could be used to study the pharmacological effect of agents on IgE production. (2) The references alone or in combination do not solve the problem of the claimed invention by providing a method treating subjects in need thereof for allergic conditions as defined on page 20 of the specification. (3) None of the references provide an effective amount of agent in a new treatment for subjects in need of treatment for allergy and hypersensitivity.

However, Roitt *et al* teach asthma is a hypersensitivity (type I) which occurs when an IgE response is directed against innocuous antigen such as pollen, the resulting release of pharmacological mediators such as histamine by IgE sensitized mast cells produces an acute inflammatory reaction with symptoms such as asthma and the levels of IgE are often raised in allergic disease (See page 19.1, page 19.3, column 2, in particular). Claims 54, 60, and 64-65 recite that the treatment is for asthma. Although Roitt et al teach hypersensitivity in general term, Tamura *et al* teach administering Escherichia coli heat-labile B subunit (LTB), also known as EtxB conjugated to allergen induced tolerance by suppression of delayed-type hypersensitivity and IgE antibody

response to allergen such as ovalbumin (See abstract, Figure 1, Table 1, Figure 2, in particular).

In response to Applicants' argument that the references alone or in combination do not solve the problem of the claimed invention by providing a method for treating subjects in need thereof for allergic conditions as defined on page 20 of the specification, although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. In re Van Geuns, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). See MPEP 2145.

In response to Applicant's argument that none of the references provide an effective amount of agent in a new treatment for subjects in need of treatment for allergy and hypersensitivity, the specific effective amount of any agent mentioned above is not recited in the claims. Further, it is within the purview of one ordinary skilled in the art at the time the invention was made to administer an "effective amount" to a subject in need of such treatment.

15. No claim is allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist (customer service) whose telephone number is (703) 872-9305.

17. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401. The IFW official Fax number is (703) 872-9306. For After Final, the Fax number is (703) 872-9307.

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